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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

FEDEX Priority Overnight #7919 1087 3901

December 1, 2000

Re: Docket No. 00D-1424 Draft Guidance for Industry
Analytical Procedures and Methods Validation

Dear Sir or Madam:

Hoffmann-La Roche hereby encloses its comments to the Draft Guidance for Industry: Analytical Procedures and Methods Validation.

Yours sincerely,

HOFFMANN-LA ROCHE INC.

Kathleen Schostack

Kathleen Schostack, Ph.D.
Director
Drug Regulatory Affairs

KS:jw
Enclosures
HLR No. 2000- 2990

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00D-1424

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Hoffmann-La Roche Inc.
Comments to FDA Draft Guidance for Industry on
Analytical Procedures and Methods Validation

Line Number	Comments
30	Clarify that the guidance is applicable to *"... supplements to these applications for new drug products."*
159	Delete *"different from, and"*. This procedure is not necessarily different.
279-281	A statement should be included that system suitability parameters that are typically used for small molecules are not always applicable to Biotech products.
287	Delete *"For example, titration...evaluation of a blank (commonly referred to as a blank titration"*. Blank titrations do not indicate the correct performance of the instrument.
324	The *"type of impurity"* is not an information of added value in the analytical procedure part. It is described in the development part of the registration dossier.
332-333	*"The total organic..."* This definition/requirement regarding QL is not in agreement with the requirements re. "Reporting Threshold" as is defined in ICH Guideline Q3A (revision).
392-393	Because the calculation formulas are provided, there is no need to show representative calculations using submitted raw data.
400-415	This information is not part of methods validation. The corresponding information is an integral part of the development portion of the registration dossier.
419-420	*"A degradation pathway..."* This information is not part of methods validation. The corresponding information is an integral part of the development portion of the registration dossier.
464-465	*"The impurity profile..."* According to ICH Q3A (revision) the term "Reporting Threshold" instead of "Quantitation Limit" should be used. The corresponding information is part of the "System Suitability Test" of the analytical procedure and not of method validation.
466-469	*"For example..."* Delete sentence. This procedure doesn't provide the desired information. Peak integrity can be better demonstrated by a technique such as diode array.
490-491	*"The analytical..."* Delete sentence. An analytical method must be appropriate for batches produced according to the registered process. It should detect differences between samples/batches of different quality, purity, etc., but it is not intended to detect process changes that do not influence product quality. It may not be suitable for batches produced according to older processes.
490-494	Information on the analytical method and sample used should be provided. However, FDA should not prescribe in exactly which form this information has to be provided.

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507-512	*"All responses...provided"* Delete sentence. Information on the analytical method and sample used should be provided. However, FDA should not prescribe in exactly which form this information has to be provided.
512-513	*"The analytical...batches."* Delete sentence. An analytical method should detect differences between samples/batches of different quality, purity, etc., but it is not intended to detect process changes that do not influence product quality.
513-514	*"The quantitation ...reported."* According to ICH Q3A (revision) the term "Reporting Threshold" instead of "Quantitation Limit" should be used.
522-580	Delete whole section. The corresponding requirements are described in ICH guideline Q2A, which should be referenced. If an update of the corresponding ICH guidelines is perceived necessary, FDA should take the initiative to provide a revision draft.
594-625	The whole paragraph VII should be a subsection of paragraph VI.
658-659	*"For ANDA ...application"* It should be clearly stated how many copies would be needed.
702-705	*"The applicant... package."* This requirement cannot be met for materials such as Impurity Standards where there are no MSDSs available.
823-824	Delete *"Frit size"* and *"Filter type"*. These materials do not have any influence on the chromatographic behavior and are not under control of the submitting company.
834ff	*"System Suitability Test"*. Refer to lines 271ff and add additional information requirements there instead of duplicating wording at two different sites.
836-840	A statement should be included that system suitability parameters that are typically used for small molecules are not always applicable to Biotech products.
862-864	Delete whole section and refer to paragraph VI for further information.
868-869	*"The effect of... procedure."* This is part of the "Ruggedness" evaluation and should be deleted here.
869-870	Delete *"The rationale for... justified."*. The use of precolumns generally serves to protect the main column. No further rationale is necessary.
883	Delete *"external diameter"*. This not useful information.
897-911	*"System Suitability Test"* Refer to lines 271ff and add additional information requirements there instead of duplicating wording at two different sites.
938	Delete *"external diameter"*. This not useful information.
959-963	*"System Suitability Test"* Refer to lines 271ff and add additional information requirements there instead of duplicating wording at two different sites.
985-993	Indicate the topic as *"Enantiomeric Excess"* in the header.
1033-1034	*"The methods validation... robustness."* The requirement to demonstrate *"intermediate precision"* is sometimes impossible to fulfill, such as in cases where only one instrument is available and/or the analysis is regularly performed on one single instrument.

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1061	Rephrase sentence as follows for clarification: *"System suitability criteria should be described for the method of analysis."*
1066	Delete "*Both the dissolution and*" since one can only validate the sampling and the analytical procedure.
1113-1125	The list is incomplete compared to the contents of the guideline. The list should be enhanced to make it usable as a checklist.

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